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ORIGINALARBEIT

Effect of different doses of erythromycin on colonic motility in patients with slow transit constipation

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SUMMARY

Background: Erythromycin has been proposed as a therapeutic agent for the treatment of functional motor disorders of the upper gastrointestinal tract. Moreover, some data exist showing a potential effect on colonic motility.

Aims: Since no data are available concerning erythromycin effects in chronically constipated patients, we investigated the effects of three different doses of the drug (50, 200, and 500 mg i. v.) on colonic intraluminal pressures in such patients.

Patients and methods: 18 severely constipated women were studied by a colonoscopically-positioned manometric probe, and were randomized to receive one of three doses of erythromycin. Proximal and distal colonic motility was recorded basally, then during placebo infusion for 60 min and for a further 60 min after the drug had been infused.

Results: Analysis of the tracings showed that, except for the lowest dose in the distal colon, erythromycin failed to stimulate colonic motility in constipated patients.

Conclusions: It is concluded that erythromycin cannot be considered a colokinetic agent, at least at doses commonly employed in the upper gut.

Key words: Colon – erythromycin – manometry – motility

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ZUSAMMENFASSUNG

(Effekt unterschiedlicher Dosierungen von Erythromycin auf die Kolonmotilität bei Patienten mit »Slow-transit-Obstipation«)

Hintergrund: Erythromycin ist als Medikament zur Behandlung funktioneller Motilitätsstörungen des oberen Gastrointestinaltraktes vorgeschlagen worden. Darüber hinaus existieren einige Befunde, die einen möglichen Effekt auf die Kolonmotilität zeigen.

Ziel: Da keine Befunde bezüglich der Erythromycinwirkungen bei chronisch obstipierten Patienten vorliegen, untersuchten wir den Einfluß von drei unterschiedlichen Dosierungen der Substanz (50, 200 und 500 mg, i. v.) auf den luminalen Druck im Kolon solcher Patienten.

Patienten und Methoden: 18 ausgeprägt obstipierte Frauen wurden mittels kolonoskopisch plazierter Manometriekatheter untersucht und erhielten in randomisierter Folge eine der drei Erythromycindosierungen. Sowohl die proximale als auch die distale Kolonmotilität wurde unter Basalbedingungen, unter Plazeboinfusion (über 60 Minuten) und über weitere 60 Minuten nach Verabreichung des Medikamentes registriert.

Ergebnisse: Die Untersuchung der Registrierungen zeigte, daß – abgesehen von der niedrigsten Dosierung im distalen Kolon – Erythromycin keinen stimulierenden Effekt auf die Kolonmotilität bei obstipierten Patienten hat.

Schlußfolgerung: In den Dosierungen, die am oberen Gastrointestinaltrakt wirksam sind, stimuliert Erythromycin die Kolonmotilität nicht.

Schlüsselwörter: Kolon – Erythromycin – Manometrie – Motilität

Due to its effects on gut motility, the macrolide antibiotic erythromycin has in the past decade been proposed as a gastrointestinal prokinetic agent (1). This compound, in fact, has been demonstrated to be active in the stomach (2) the gallbladder (3), and the small bowel (4). Erythromycin's ability to accelerate gastric emptying (5) led also to its use in diabetic gastroparesis (6). Erythromycin is now known to be a motilin receptor agonist (7) and these prokinetic effects are assumed to be due to a direct action on smooth muscle motilin receptors (8, 9). In fact, the contractile ability of erythromycin varies between the different regions of the

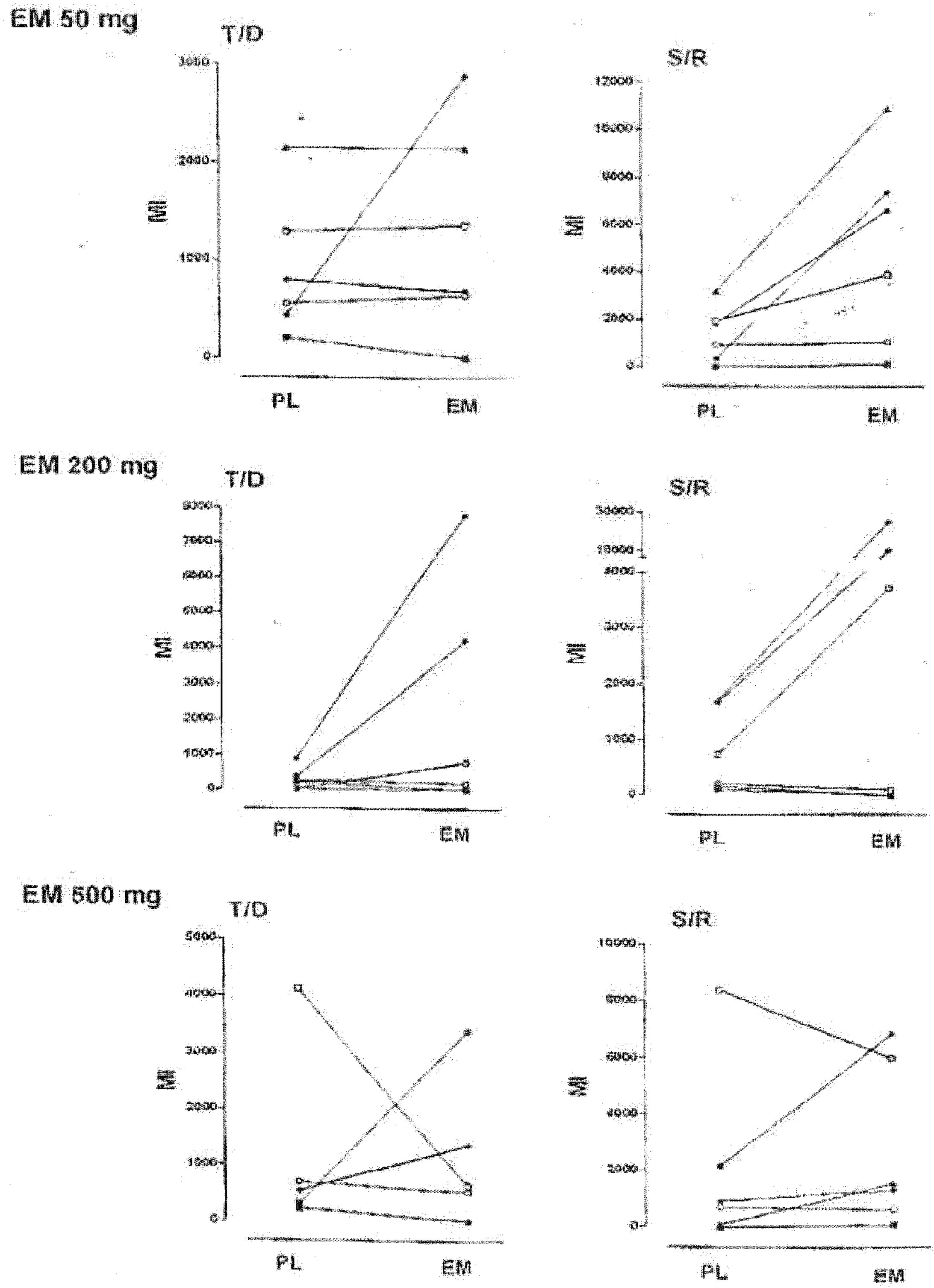

Fig.: Individual Motility Indexes (MI) at different erythromycin i. v. doses (50, 200, and 500 mg) in proximal (T/D) and distal (S/R) colonic segments

lowed by infusion of placebo (250 ml saline in 15 min), and a further 60 min recording. Finally, three groups of six patients each were randomized to receive either 50, 200, or 500 mg i. v. erythromycin in 250 ml saline, infused over a period of 15 min. The recording was continued for 60 min, after which the study session was stopped. Patients were blind to when the drug versus the placebo (which appeared identical to the drug) were given. Throughout the study, one of the investigators closely monitored the subjects for the presence of side effects.

DATA ANALYSIS

All tracings were coded and analyzed manually in blind by one of the investigators. A Motility Index (MI)/60 min was calculated separately for proximal (data obtained from transverse and descending colon) and distal (data obtained from sigmoid colon and rectum) colonic segments during placebo infusion and after erythromycin administration, by measuring the amplitude and duration of each pressure wave and then multiplying half the mean amplitude of pressure waves by the sum of their duration (24, 25). This formula estimates the area under the curve by assuming that pressure waves are triangular in shape. In order to avoid including respiratory artifacts, only pressure waves of amplitude greater than10 mmHg were taken into account for calculations. Due to their spike-like appearance at all recording ports, movement artifacts were also easily recognized and discarded.

STATISTICAL ANALYSIS

Due to the skewed distribution of the data, nonparametric tests were adopted for calculations. For each subject, the MI from proximal and distal colonic segments, pre- (placebo) and posterythromycin were compared by the Wilcoxon rank sum test. Values of p less than 0.05 were chosed for rejection of the null hypothesis. Unless differently specified, data are presented as medians (range). Statistical analysis was carried out by the BMDP statistical software (26).

RESULTS

During placebo infusion, the overall MI (represented by segmental-type waves) was significantly lower in the proximal than in the distal colonic segments (means ± SEM, 728 ± 233 vs. 1,400 ± 465, p = 0.018). After erythromycin injection, no dose employed was able to stimulate effectively colonic motility (tab., fig.), except the dose of 50 mg in the distal segments.

The type of contractile activity associated with erythromycin injection was low-amplitude, nonpropagated waves (segmental type). No high-amplitude propagated contractions, the manometric equivalent of mass movements (27), were recorded in any colonic segment after erythromycin was injected.

Side effects were reported by four patients after erythromycin injection, all after the higher doses (500 mg), and were represented by nausea and mild epigastric cramps.

DISCUSSION

This is the first study to assess objectively the effects of erythromycin as a possible colokinetic agent in chronic constipation. Erythromycin, in doses ranging from 50–500 mg, failed to stimulate colonic motility in patients with severe chronic constipation. The only significant variation we observed was at the distal colonic level with the lowest dose investigated (50 mg). This low dose was associated with an increase in segmental-type contractions. Although a β error could not be excluded, looking at the individual responses in all segments (fig.) we feel that these data might be extrapolated to a larger number of patients. In fact, the trend for most patients was consistently toward minimal or no response to i. v. infusion of the drug. More importantly, high-amplitude propagated contractions, the manometric equivalent of mass movements, a physiologic event closely related to defecation, were never observed following erythromycin injection.

Previous manometric studies in healthy subjects showed no effect of erythromycin on colonic motility (15), or an increase in MI only in the sigmoid colon, which was smaller than that observed after a meal (16). A colonic myoelectric study in patients with irritable bowel syndrome also reported no effect of erythromycin in proximal and distal segments of the viscus (17). Colonic transit studies have been inconsistent. In healthy volunteers, oral erythromycin had no effect on segmental or total colonic transit time in one study (15), but other authors reported a significant decrease of transit time in the right colon, even though the total colonic transit time was not significantly decreased (28) A recent pilot study evaluating the effect of oral erythromycin in patients with idiopathic constipation showed that the drug shortened the total colonic transit time, and segmental transit studies revealed a significant effect only in the right colon and rectosigmoid area (18). However, it is possible that these effects were secondary to a stimulation of upper gut motor activity (29) or to an antibacterial action of erythromycin (18).

As in other studies, most of the (limited) side effects were observed with higher doses of erythromycin; this, and the fact that almost all the few positive effects on colonic motility were observed with the lower doses, should stimulate further research on the possible stimulatory effects of low-dose erythromycin in functional constipation.

Although a note of caution in interpreting this and other studies concerning colonic motility seems wise, in that they require colonic preparation, there is now convincing evidence that the prepared colon, from its motor point of view, behaves in a close manner to the unprepared viscus, especially concerning segmental-type (i. e., the predominant) contractile activity (30).

In conclusion, erythromycin at different i. v. doses does not stimulate colonic motility in patients with severe chronic constipation. However, other macrolides that display action in the upper gut (31, 32) may in the future be demonstrated as colokinetic agents.

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